Implementing Metrological Traceability in Laboratory Medicine: NCCLS Role

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NCCLS 2004 Leadership Conference

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NCCLS/IFCC Joint Project on Metrological Traceability

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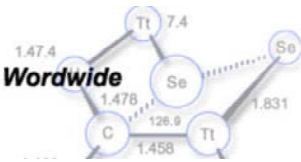
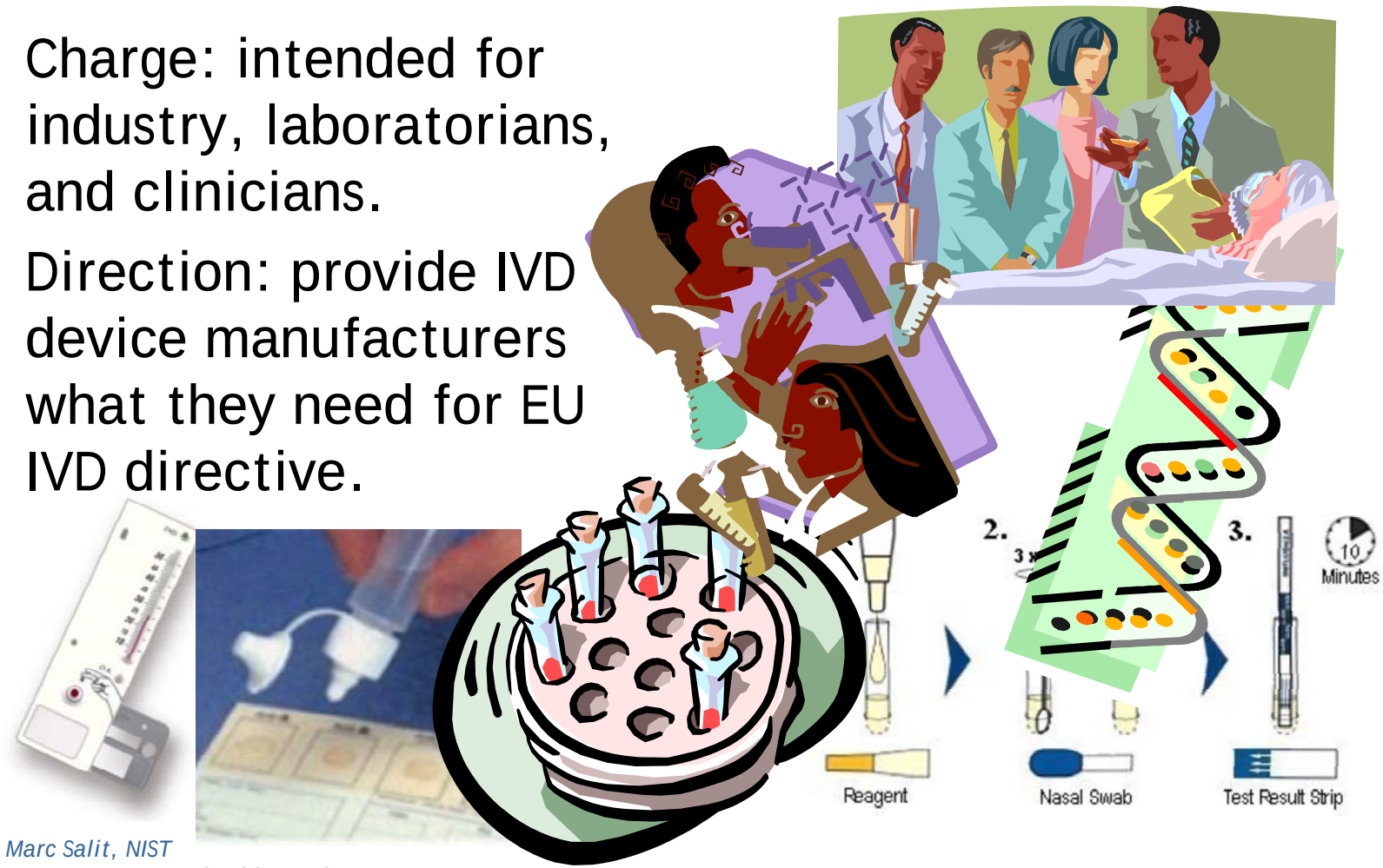
IFCC International Federation of Clinical Chemistry and Laboratory Medicine
Serving Laboratory Medicine Wordwide



- Team formed Sept. 2003 to develop a report
  - explaining traceability
  - explaining how traceability is established
  - discussing benefits of traceability
  - outlining a reference system
    - roles of reference materials
    - reference procedures
    - reference laboratories
    - laboratory networks

Intended Audience

- Charge: intended for industry, laboratorians, and clinicians.
- Direction: provide IVD device manufacturers what they need for EU IVD directive.



Membership

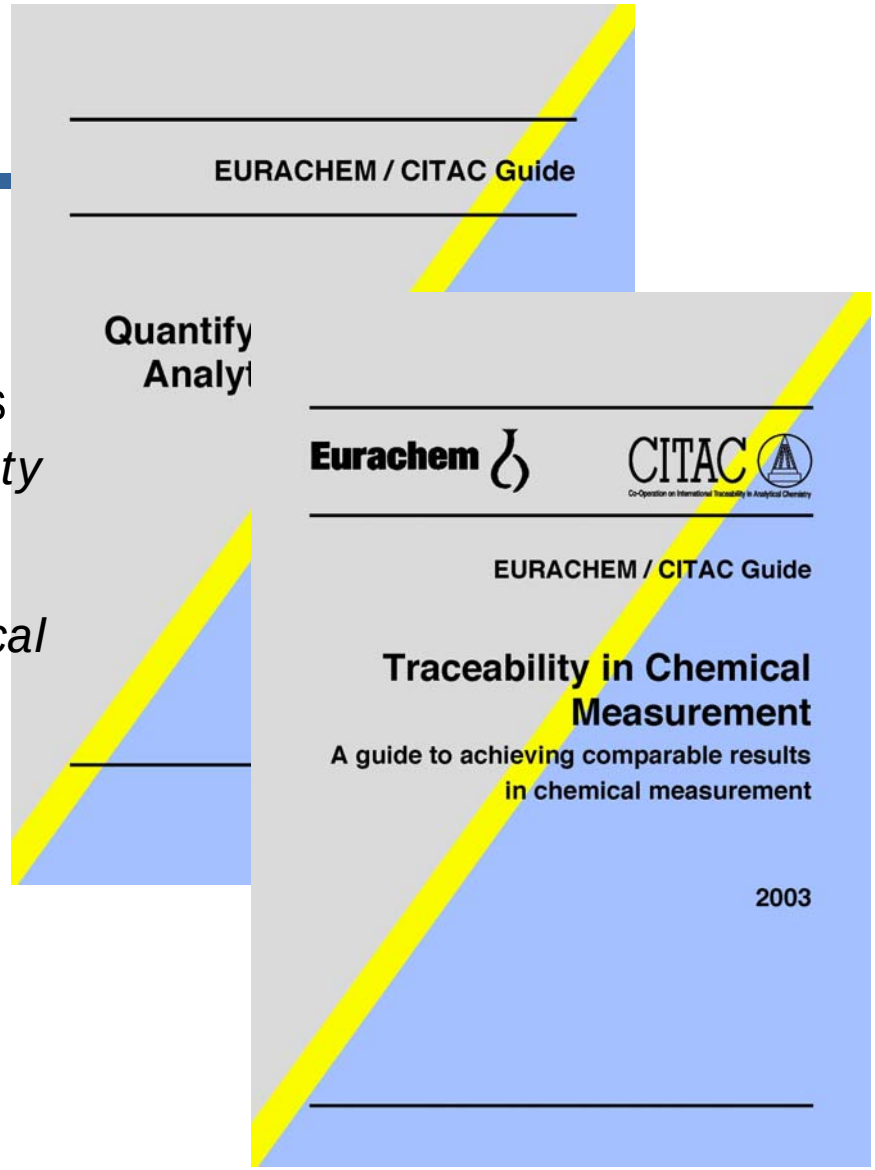
- joint responsibility of IFCC and NCCLS
- working group
  - NIST and BIPM
  - representatives designated by IFCC and NCCLS
    - clinical laboratorians

Members

- Marc Salit, Ph.D.
  - Chairholder, NIST
- Dr. Thomas Ciesiolka
  - Roche Diagnostics GmbH
- Neil Greenberg, Ph.D.
  - Ortho-Clinical Diagnostics
- Richard R. Miller, Jr.
  - Dade-Behring
- W. Gregory Miller, Ph.D.
  - VCU
- Gary L. Myers, Ph.D.
  - CDCP
- Prof. Mauro Panteghini
  - Azienda Ospealiera “Spedali Civil”
- Prof. Gerhard Schumann
  - Medizinische Hochschule Hannover
- Professor Dr. Lothar Siekmann
  - University of Bonn
- David Sogin, Ph.D.
  - Abbott Laboratories
- Geraldine L. Barnes, M.T.(ASCP), M.S.
  - Project Manager, NCCLS

Strategy

- leverage existing practical guidance
  - Eurachem/CITAC guides
    - *Quantifying Uncertainty in Analytical Measurement*
    - *Traceability in Chemical Measurement*
- amplify where needed for clinical context
  - address commutability
  - include examples

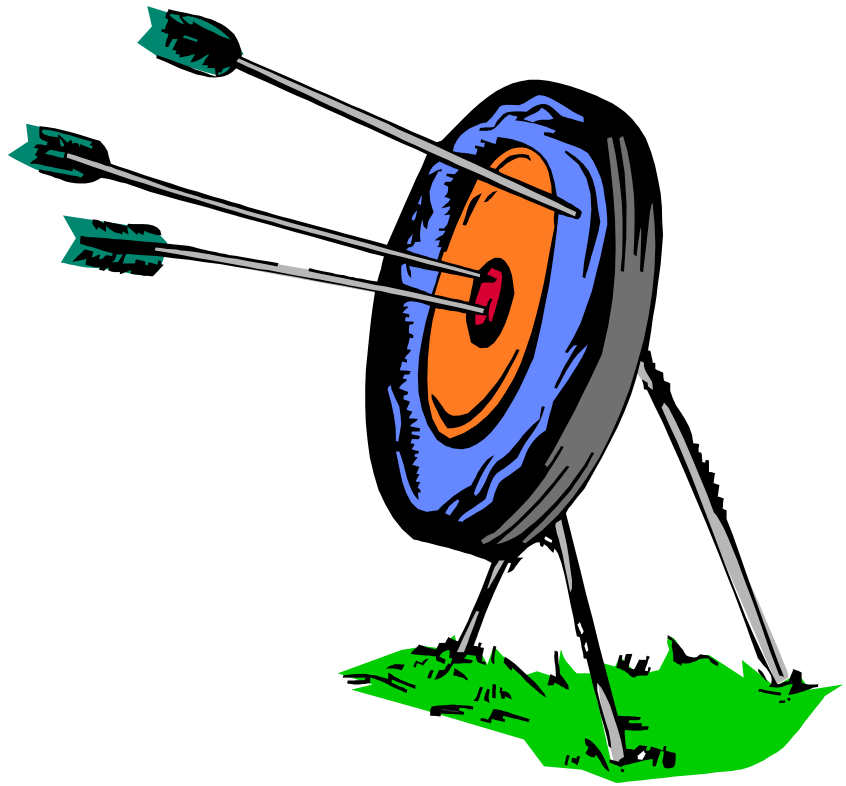


NCCLS/IFCC Guide Structure

- Scope
- Introduction
  - Quality in Clinical Measurement
  - External Environment
- Definitions and Terms
- Traceability
  - Overview of the process for establishing traceability
  - Process of establishing traceability
  - Reporting traceability
- References
- Appendices
- Quality System Approach
- Examples
  - Glucose
  - ALT
  - HCG
  - Matrix effects

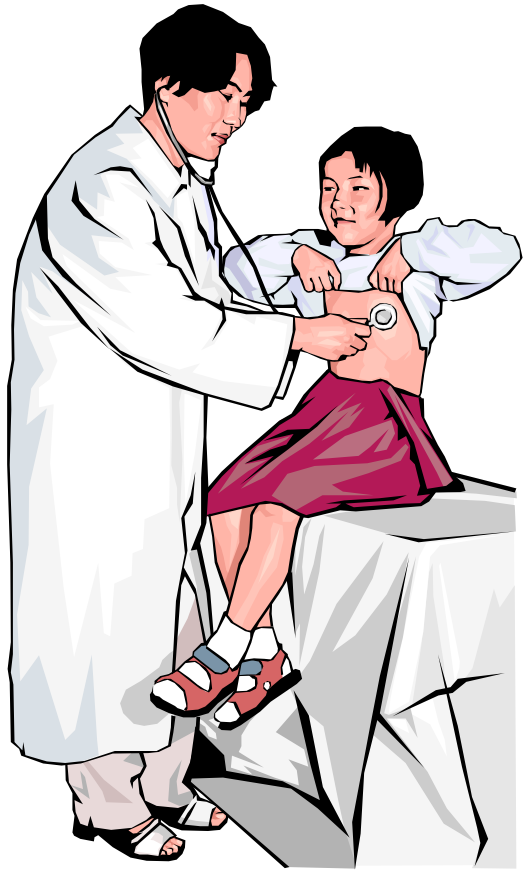
Scope

- "The primary area of activity to which the principles of this report may be applied…"
  - determination of "assigned" values for calibrators and trueness controls for IVD measurement devices
  - traceability of measurement results for certification of reference materials that support IVD device manufacture



Introduction

- Context of laboratory medicine in health care
  - information must be
    - independent of test kit
    - instrument
    - device
- Harmonization of results
  - results must be comparable within and between different parts of the enterprise



Quality in Clinical Measurement

- *For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and that the results reported to the physicians or other health care personnel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.*

  Introduction, ISO 17511

- *adequately defined and … adequately accurate (true and precise)…*
  - Method Validation
    - to establish trueness
  - Uncertainty
    - to establish precision
- *comparability over space and time*
  - Traceability
    - enable comparability

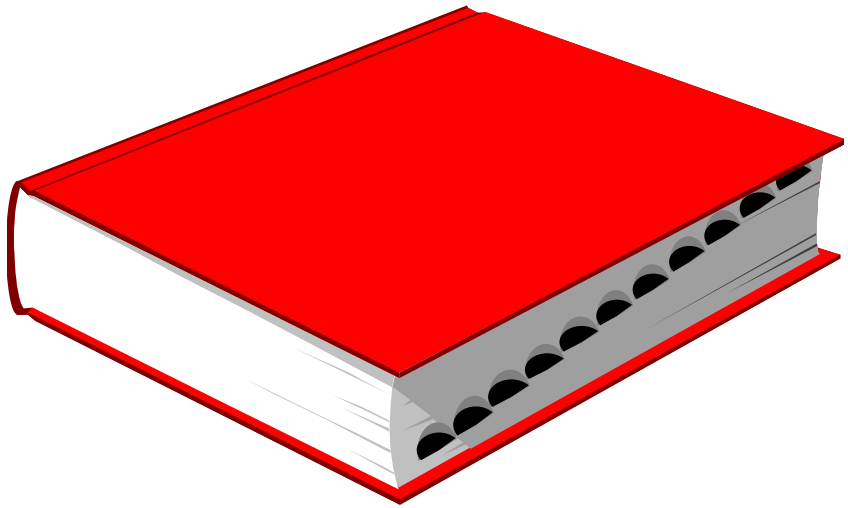
External Environment

- Adoption of quality systems in Laboratory Medicine
  - IVD Device Directive
  - JCTLM formed to address needs
    - guidance for reference materials and methods
    - sponsored by BIPM
    - NMIs, accreditation, regulators, IVD device manufacturers

- Standards documents
  - 17511
    - Traceability Targets Manufacturers
  - 18153
    - Catalytic Concentration of Enzymes
  - 17025
    - Testing and Calibration Laboratories
  - 15189
    - Testing in Medical Laboratories
  - 15193
    - Reference Measurement Procedures
  - 15194
    - Reference Materials for Biological Samples
  - 15195
    - Reference Laboratories for Laboratory Medicine

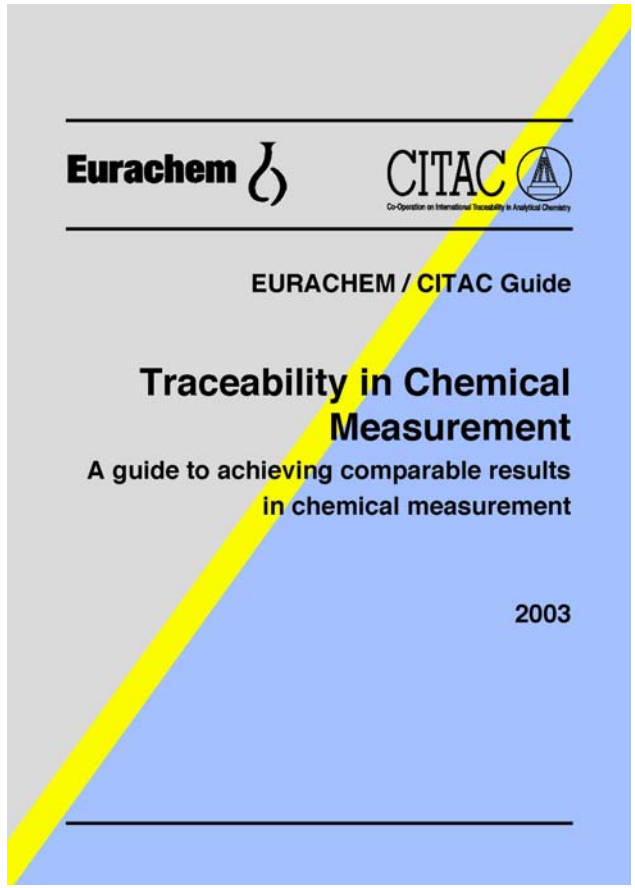
Definitions and Terms

- compilation of useful terms
  - multiple standards documents referenced
  - *no new definitions*



Traceability

To achieve comparability of results over space and time, it is essential to link all the individual measurement results to some common, stable reference or measurement standard. Results can be compared through their relationship to that reference. This strategy of linking results to a reference is termed "traceability."



Measurement model

$$C_{Unknown} = \frac{C_{Standard}}{S_{Standard}} S_{Unknown}$$

- Eurachem/CITAC guide suggests:
  - measurement equation to define the measurand
    - provides a means to calculate the value of the measurand in terms of other measured quantities
    - traceability is established by ensuring all these measured quantities are themselves traceable
  - validation process demonstrates the equation's completeness

Establishing Traceability

- Specification of the measurand
  - scope of the measurements
  - required uncertainty
- Selection of a suitable method
  - estimate the measurand
- Validation
  - demonstrate that all significant influences appear in the measurement equation
- Identify relative importance of influence quantities
- Select appropriate reference standards
- Estimate the uncertainty

Measurand Specification

- Care must be taken to establish and specify what is being measured
  - antibody-epitope interaction in antibody tests
    - PSA by various assays can differ because of differences in antibodies
  - HCG *as tumor marker*
    - wouldn't want to establish HCG assay against WHO standard
      - prepared from urine of pregnant women

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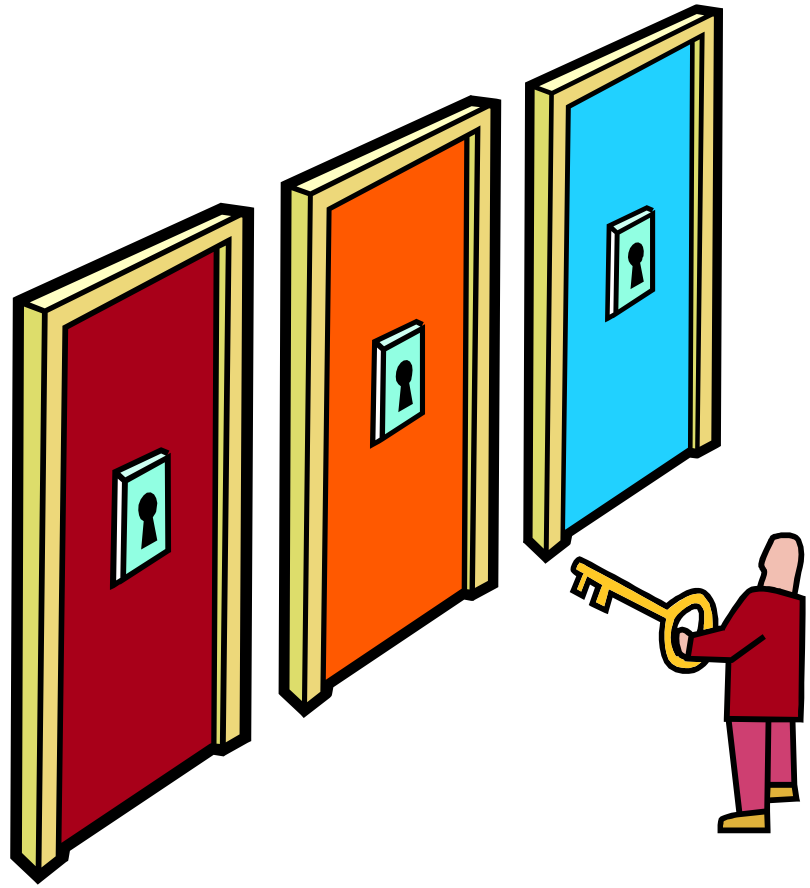
Method Selection

- Coupled to…
  - measurand specification
  - accepted performance requirements
  - fitness for purpose
  - business case



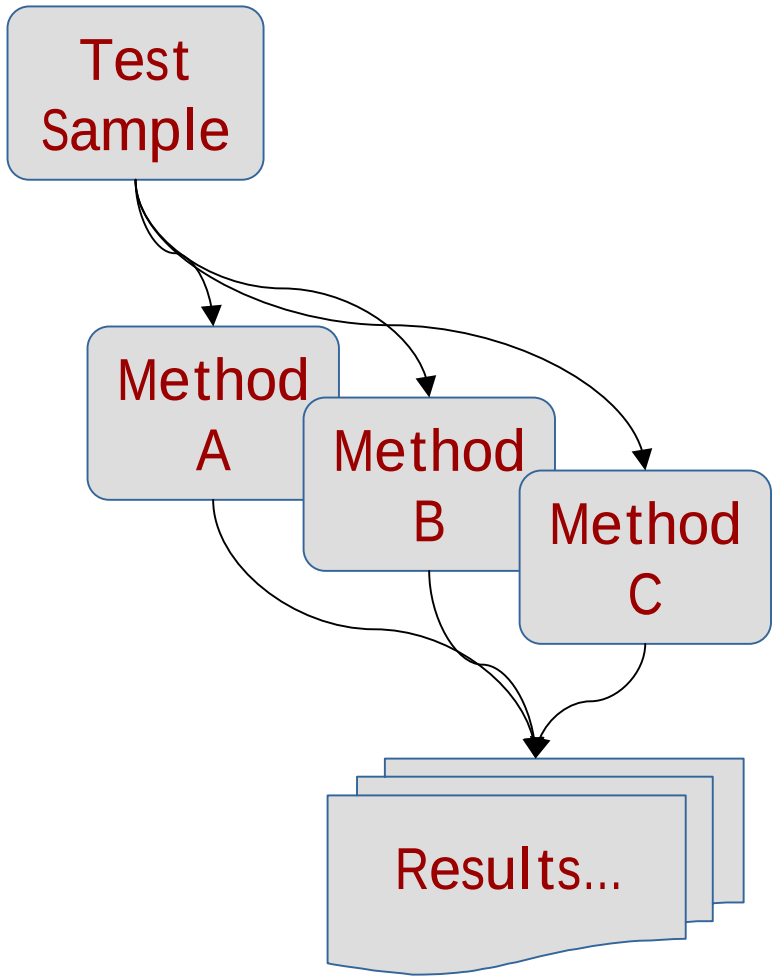
Validation

- Chemical measurements are comparisons
  - methods transfer a value from a reference to an unknown
- Validation establishes fitness for purpose of transfer steps
  - uncertainty
  - interferences
  - commutability
    - human samples
    - manufacturer's product calibrator & routine procedure v. reference procedure
      - ref. 17511/18153 for method comparisons

Commutability

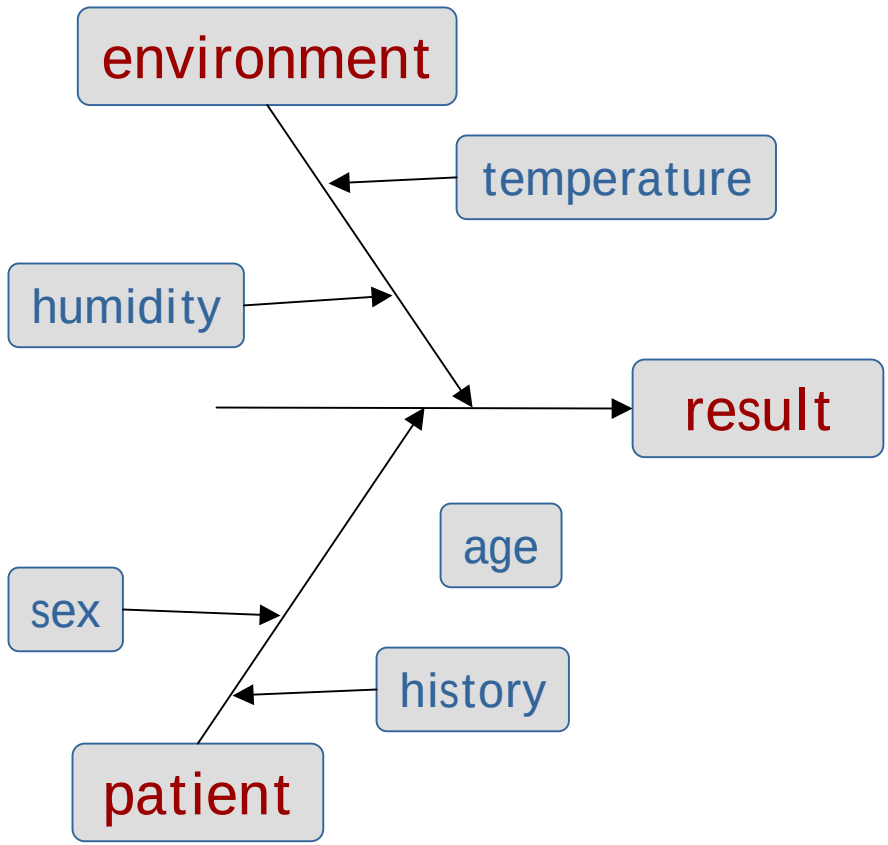
"closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples"

ISO 17511:2003(E), ¶3.9



Influence Quantities

- factors in the measurement model or environment that need to be measured or controlled
  - patient
    - history
    - age
    - sex
  - lab conditions
    - temperature
    - humidity



Selection of References

- "higher-order"
  - JCTLM to deliver credentialed…
    - reference materials
    - reference procedures
    - reference laboratories
- commutability
  - as appropriate, throughout the calibration hierarchy
    - absence of matrix effects
- reference to NCCLS EP-14A
  - Evaluation of Matrix Effects: Approved Guideline

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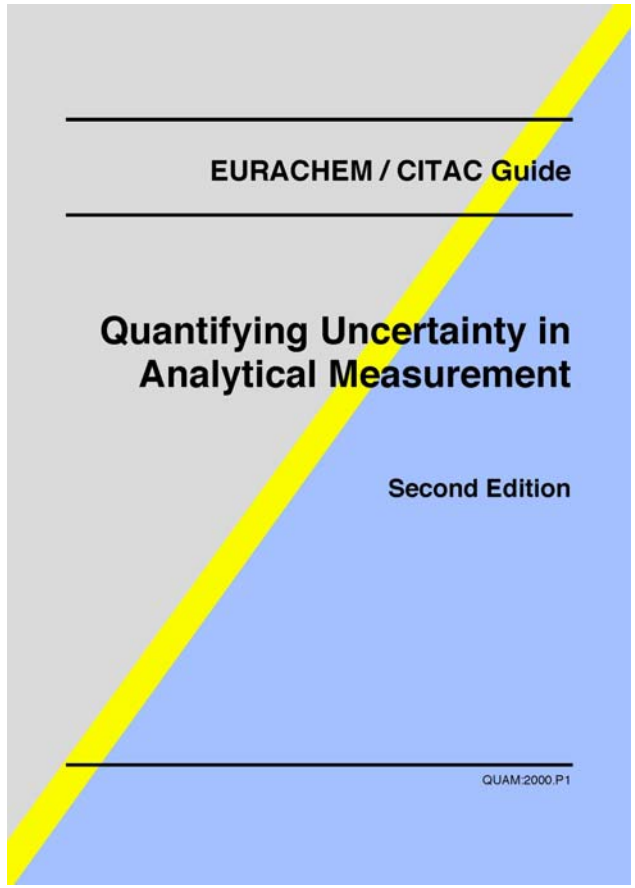
Uncertainty

- Defer/refer to Eurachem/CITAC Guide
  - Quantifying Uncertainty in Analytical Measurement, 2nd Edition
  - Examples will reference sections



Examples in development

- Glucose
  - clearly defined analyte, traceabilty chain
- ALT
  - Alanine aminotransferase
  - commutability issues
- HCG
  - human chorionic gonadatropin
  - immunoassay of large molecule
- Matrix effects
  - evaluation of matrix effect with NCCLS EP-14

Next Steps

- Further development and refinement of examples
- Integration of examples
- Broad circulation of draft
  - 26 March telecon
  - 29 April telecon